

Effect of a concomitant diagnosis of allergic rhinitis on asthma-related health care use by adults

D. Price*, Q. Zhang†, V. S. Kocevar†, D. D. Yin† and M. Thomas*

*Department of General Practice and Primary Care, University of Aberdeen, Foresterhill Health Centre, Aberdeen, UK and †Merck & Co. Inc., Worldwide Outcomes Research Department, Whitehouse Station, NJ, USA

Summary

Background Asthma and allergic rhinitis (AR) frequently coexist, but have usually been studied separately in health economic analyses.

Objective To determine the incremental effect of documented AR on health care resource use in adults with asthma.

Methods A retrospective cohort study using data from a UK general practice database for the period 1998–2001 enrolled subjects 16–55 years of age, with one or more asthma-related general practitioner (GP) visits during a 12-month follow-up period. The study outcomes were asthma-related hospitalizations, GP visits, and prescription drug costs during the 12-month follow-up period for patients with and without physician-diagnosed AR.

Results Concomitant AR was documented in 4611 (16.9%) of the total sample of 27 303 adults with asthma. Compared with those with asthma alone, patients with concomitant AR experienced more GP visits (5.2 vs. 4.2; $P < 0.0001$) and more of them were hospitalized for asthma (0.76% vs. 0.45%; $P < 0.01$) during the 12-month follow-up period. In multi-variable regression analyses, AR was predictive of hospitalization for asthma (odds ratio 1.52, 95% confidence interval (CI) 1.03–2.24) and was associated with an increase in the annual number of asthma-related GP visits (mean increase per patient 0.42, 95% CI 0.42–0.43) and annual asthma-related drug costs (mean increase GBP 5.1, 95% CI 5.0–5.3).

Conclusion Adults with asthma and documented concomitant AR experienced more asthma-related hospitalizations and GP visits, and incurred higher asthma drug costs than did adults with asthma alone. A unified treatment strategy for asthma and AR might reduce the costs of treating these conditions.

Keywords adults, allergic rhinitis, asthma, medical resource use

Submitted 29 April 2004; revised 29 July 2004; accepted 17 December 2004

Introduction

Allergic rhinitis (AR) and asthma are highly prevalent, chronic respiratory diseases, both of which are associated with substantial economic costs. Between 3% and 19% of adults in western countries are diagnosed with asthma [1]. One of the highest prevalences occurs in the United Kingdom, where the prevalence of currently treated adult asthma is 7% [2]. Emergency care, i.e. an Emergency Department (ED) visit or hospitalization, is a key component of asthma treatment costs. In studies of the cost of asthma in six countries (United Kingdom, United States, France, Sweden, Canada, and Australia), ED visits and hospitalizations constituted about one-third of total direct costs (median 30%, inter-quartile range 24–52%) [3]. More recent studies from France, Estonia, Canada, and Singapore reported values in the same range [4–7] and studies of adults with asthma in the United States

and Switzerland indicated that between 30% and 45% of direct medical costs were for emergency care [8–11].

AR is present in up to about 40% of individuals in different populations [12]. The prevalence of perennial rhinitis among adults in the United Kingdom is 9–13% [12]. Although patients often have a significant burden of symptoms because of AR, emergency care for AR is not a significant component of treatment costs. Available data for the direct costs of AR refer to studies of the overall population in the United States, where ED visits constituted only 1.3–1.5% of direct medical costs (no hospitalizations were reported) [13, 14]. The total direct cost of AR in these studies was \$1.2–3.4 billion, compared with \$6.1 billion for asthma [8].

AR and asthma are linked epidemiologically, pathophysiologically, and therapeutically, and can be considered as different manifestations of a single inflammatory airway syndrome [15]. Epidemiological studies have shown that asthma and AR frequently coexist, and that AR usually precedes asthma and can be considered a risk factor for the development of asthma [16]. Asthma is present in about 40% of adults with rhinitis, while rhinitis occurs in up to 80% of

Correspondence: Dr Vasilisa Sazonov Kocevar, Merck & Co. Inc., WS2E-50, One Merck Drive, PO Box 100, Whitehouse Station, NJ 08889-0100, USA. E-mail: Vasilisa_sazonovkocevar@merck.com

patients with asthma [16, 17]. Certain medications, e.g., corticosteroids and anti-leukotrienes, are effective in treating both asthma and rhinitis.

The Allergic Rhinitis and its Impact on Asthma (ARIA) initiative, developed in collaboration with the World Health Organization, recommends that a combined treatment strategy be used to treat upper and lower airway diseases [12, 15]. A unified treatment strategy for asthma and AR might reduce the costs of treating these conditions. However, there is little information about the direct medical costs of combined asthma and AR, because cost-of-illness studies have usually considered them as two separate conditions. The objective of this report is to analyse the direct medical costs of asthma and documented concomitant AR compared with asthma alone, and to determine whether AR is associated with increased treatment costs for asthma.

Methods

Study description

This was a historical cohort study. Medical resource use data were obtained from the UK MediPlus® (London, UK) database, which contains diagnosis and prescribing information for more than one million patients from a nationally representative sample of over 500 general practitioners (GPs) [18]. The study consisted of three time periods: a 3-year diagnostic period, a 6-month baseline period, and a 12-month follow-up period. Records of a diagnosis of AR or prescriptions indicating AR were sought during the 3-year diagnostic period (1 October 1998 to 30 September 2001). In the baseline period (1 April 2000 to 30 September 2000), patient characteristics and the historical use of asthma-related drugs were determined. Study outcomes were determined for the follow-up period between 1 October 2000 and 30 September 2001.

Identification of asthma and allergic rhinitis

Patients were included in the study if they were between the ages of 16 and 55 years during the diagnostic period and had one or more asthma-related GP visits during the 12-month follow-up period. An asthma-related GP visit was defined by Read diagnostic codes for asthma (H43), extrinsic asthma atopy (H431), intrinsic asthma (H432), status asthmaticus (H433), asthma attack not otherwise specified (H434), asthma not otherwise specified (H43Z), or history of asthma (14B4). A patient was classified as having documented AR if one or more AR diagnoses or prescriptions indicating AR were recorded during the 3-year diagnostic period. A diagnosis of AR was defined by codes for hayfever (H28), AR not otherwise specified (H29), or a history of hayfever (14B1). AR-related prescriptions were identified using ATC codes for systemic antihistamines (R06A0), nasal corticosteroids without anti-infectives (R01A1), nasal corticosteroids with anti-infectives (R01A3), nasal anti-allergic agents (R01A6), and nasal decongestants (R01A7).

Study variables

Patient demographics and asthma-related drug use in the baseline period were considered as co-variables in the analysis

of health care resource use during the follow-up period. Baseline co-variables were: patient age, sex, oral corticosteroid use, number of short-acting β -agonist (SABA) prescriptions, and dosage of inhaled corticosteroids, classified as low, medium, or high, as defined in the Global Initiative for Asthma guidelines [1]. The study outcome variables were: asthma-related hospitalizations, GP visits, and prescription drug use and costs. Prescription drugs included quick-relief medications (SABAs and inhaled corticosteroids), long-term preventive medications (inhaled corticosteroids, anti-leukotrienes, long-acting β -agonists, cromoglycate, and theophylline), and antibiotics. The dose of inhaled corticosteroids and the number of SABA prescriptions were used as surrogate measures of asthma severity [19]. Drug costs were estimated by multiplying the number of prescriptions by the unit cost, obtained from IMS. IMS prices for April 2001 (the midpoint of the follow-up period) were used; September 2001 (the last month of follow-up) prices were used for items that were unavailable in April 2001.

Statistical analysis

The *t*-test was used for continuous data and the χ^2 test for discrete data in the comparisons of baseline characteristics and unadjusted study outcomes in adults with and without AR. A logistic regression analysis was developed with asthma-related hospital admission during the follow-up period as the response variable and concomitant AR and baseline patient characteristics as explanatory variables. Linear regression analyses were performed with the number of asthma-related GP visits and drug costs as response variables and concomitant AR as the explanatory variable, controlling for baseline patient characteristics. The number of GP visits and drug costs were log transformed to correct for their non-normal distributions. The bootstrap re-sampling method was used to estimate confidence intervals (CIs) of the predicted mean difference in the number of GP visits and drug costs [20]. Bootstrapping estimates were adjusted for patient age, smoking status, baseline use of oral corticosteroids, baseline dose of inhaled corticosteroids, and the number of prescriptions for SABAs (gender was not statistically significant in the linear regression models). A *P*-value of 0.05 was considered to be statistically significant. All statistical analyses were performed using SAS v8.2 (Cary, NC, USA).

Results

Baseline characteristics

A total of 27 303 adults met the study criteria and were included in the analysis: 22 692 (83.1%) had asthma only and 4611 (16.9%) had both asthma and documented AR (Fig. 1). The average age was about 34 years, about 56% were women, and about 6.5% were current smokers (Table 1). The use of asthma medications during baseline period – SABAs, oral corticosteroids, and inhaled corticosteroids – was statistically significantly greater among subjects with asthma and concomitant AR than among subjects with asthma alone ($P < 0.0001$).

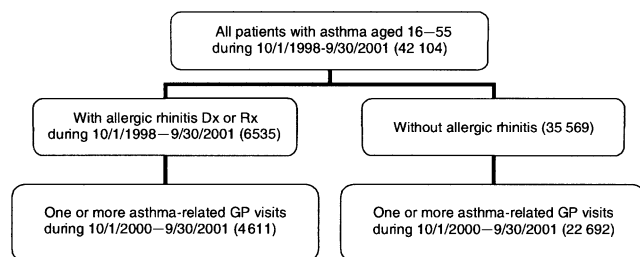


Fig. 1. Study flow diagram.

Table 1. Baseline characteristics of patients with and without AR

	Asthma alone	Asthma and AR	P-value
N	22 692	4611	
Age, mean years (SD)	33.9 (11.3)	33.2 (11.5)	<0.0001*
Women (%)	55.9	54.5	NS†
Current smoker (%)	6.6	5.9	NS†
SABA prescriptions, mean number (SD)	1.2 (2.0)	1.5 (2.4)	<0.0001*
Oral corticosteroid use (%)	4.3	6.9	<0.0001†
Inhaled corticosteroid dosage (%)			<0.0001†
No usage	63.0	56.1	
Low	27.2	31.5	
Medium	8.4	10.7	
High	1.3	1.8	

SABA, short-acting β -agonist; AR, allergic rhinitis.**t*-test. † χ^2 test.

Effect of a concomitant diagnosis of allergic rhinitis on general practitioner visits and hospitalizations

Patients with documented AR visited the GP significantly more often for asthma than did adults with asthma alone: the mean (SD) number of GP visits during the 12-month follow-up period for patients with asthma and AR was 5.2 (5.5), compared with 4.2 (4.5) for patients with asthma alone ($P < 0.0001$, *t*-test). After adjusting for the baseline characteristics in the multi-variable linear regression analysis, patients with both asthma and AR had an average of 3.8 visits in the 12-month follow-up period, compared with 3.4 GP visits for patients with asthma alone, a least-squares mean difference of 0.42 (95% CI 0.42–0.43; $P < 0.0001$).

Patients with documented AR were significantly more likely to be hospitalized for asthma during the 12-month follow-up period. The percentage of patients with asthma and AR with asthma-related hospitalizations was 0.76, compared with 0.45 for those with asthma alone ($P = 0.0058$, χ^2 test). After adjusting for other variables in the multi-variable analysis (Table 2), concomitant AR increased the odds of hospitalization for asthma by about 50% (odds ratio 1.52, 95% CI 1.03–2.24). Other statistically significant predictors of hospitalization for asthma were female sex and cigarette smoking, as well as the use of medium- or high-dose inhaled corticosteroids, oral corticosteroids, and greater use of SABA (which are surrogate measures of asthma severity) during the baseline period (Table 2).

Table 2. Logistic regression analysis: likelihood of asthma-related hospitalization

Variable	Odds ratio	95% confidence interval	P-value
Allergic rhinitis	1.52	1.03–2.24	0.0365
Female	1.56	1.09–2.22	0.0155
Current smoker	2.81	1.79–4.41	<0.0001
Number of SABA prescriptions*	1.15	1.10–1.21	<0.0001
Oral corticosteroid use*	3.01	1.90–4.78	<0.0001
Inhaled corticosteroid use: medium dose*	1.76	1.13–2.74	0.0119
Inhaled corticosteroid use: high dose*	2.26	1.04–4.94	0.0408

SABA, short-acting β -agonist.

*Asthma drug use recorded during the baseline period.

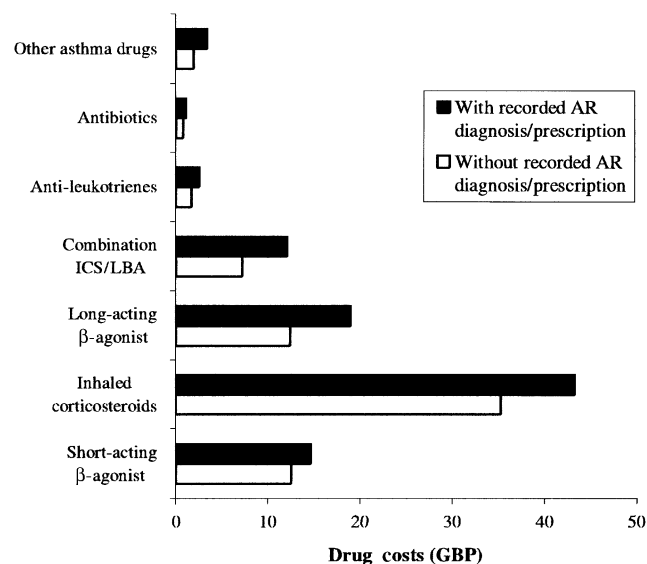


Fig. 2. Costs of asthma-related drugs by drug class.

Effect of a diagnosis of allergic rhinitis on drug use and costs

Patients with concomitant AR filled significantly more prescriptions for SABAs and oral corticosteroids during the 12-month follow-up period than did adults with asthma alone. The mean (95% CI) number of SABA prescriptions for patients with asthma and AR was 3.15 (3.02–3.27), compared with 2.71 (2.66–2.75) for patients with asthma alone ($P < 0.0001$, *t*-test). Corresponding values for oral corticosteroid prescriptions were 0.195 (0.171–0.220) and 0.149 (0.140–0.158), $P = 0.0006$, *t*-test).

In the multi-variable linear regression analysis, a concomitant diagnosis of AR was a significant predictor of higher annual costs for asthma medications ($P = 0.0001$). Patients with asthma alone had average drug costs of GBP 65.0, while patients with asthma and AR had average drug costs of GBP 70.2: least-squares mean difference 5.1 (95% CI 5.0–5.3). Patients with concomitant AR incurred greater costs for all categories of prescription asthma medications than did patients with asthma alone (Fig. 2). Patients with concomitant AR incurred higher costs for asthma-related drugs

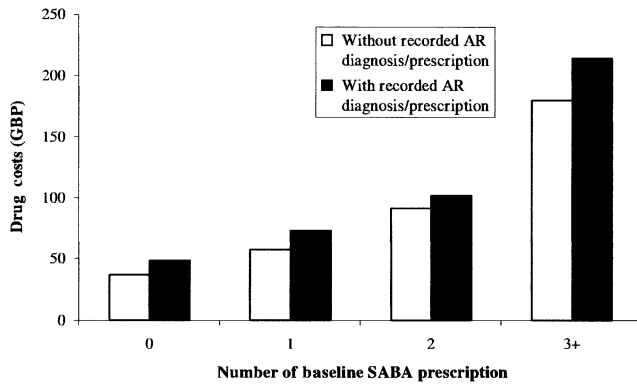


Fig. 3. Cost of asthma drugs by baseline use of short-acting β-agonists.

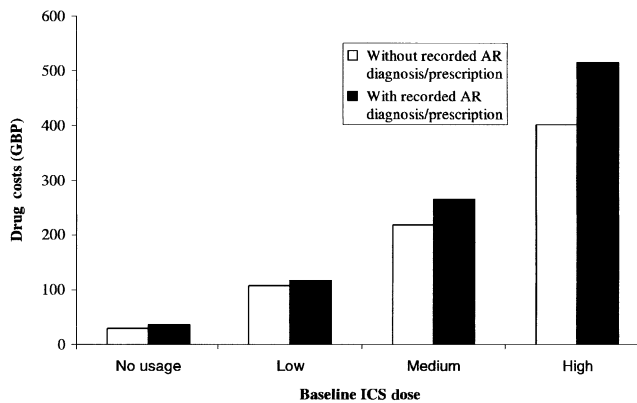


Fig. 4. Cost of asthma drugs by baseline use of inhaled corticosteroids.

regardless of the severity of asthma, as indicated by use of SABAs (Fig. 3) or of inhaled corticosteroids (Fig. 4) during the baseline period.

Discussion

In this retrospective cohort study based on a general practice database, we determined the effect of documented concomitant AR on asthma-related medical resource use by over 27 000 adults with asthma in the United Kingdom. Those with concomitant AR consumed more asthma-related health care resources, in terms of GP visits, hospitalizations, and prescription medication costs than did patients with asthma alone. These results were consistent across different levels of asthma severity as assessed indirectly by analyses based on the intensity of asthma drug use.

The prevalence of documented AR in this population of patients with asthma was low (16.9%) compared with that reported in epidemiological studies [16]. This may be explained by several factors: first, many cases of AR in the community are undiagnosed; second, AR is frequently self-managed by patients without discussion with their primary care physician; and third, the symptoms may be too mild to bother the patient sufficiently to prompt treatment or consultation. Hence, the patients with documented concomitant AR in the primary care population studied here are likely to represent those with more severe disease or those with more bothersome symptoms.

The findings reported here for adults are similar to results for children in a companion study based on the same general practice database [21]. The association between concomitant AR and hospitalization for asthma was stronger among children (odds ratio 2.34, 95% CI 1.41–3.91; $P = 0.001$). This difference reflects a greater risk of hospitalization among children with asthma: 1.4% of children with concomitant AR were hospitalized, compared with 0.8% of adults with both conditions and 0.45–0.5% of children or adults with asthma alone. The effect of concomitant AR on GP visits (an increase of about 0.4–0.5 visits per subject) was similar in both adults and children.

There are few data with which to compare the results of this study [22–24]. A US study of 1245 patients with asthma, about half of whom had concomitant AR, found no consistent association between AR and total medical charges among adults, but did not report medical costs specifically related to asthma [22]. A German study that included 224 adults with asthma and/or seasonal AR found no consistent relationship between concomitant AR and medical service use [24]. The relatively small sample size of that study might have resulted in an underestimation of the costs of emergency care for asthma, which though costly is relatively infrequent. Results of a retrospective, cross-sectional analysis of medical claims data from a US health insurance plan were generally similar to those of the present study [23]. Thirty-four percent of 27 398 subjects with asthma also had a diagnosis of AR. Adults with concomitant AR exhibited higher rates of use of asthma drugs (inhaled β-agonists, inhaled and oral steroids, inhaled cromones) and about a 3-fold higher rate of outpatient episodes linked to asthma, AR, or related conditions. Hospitalizations for asthma or related conditions were not, however, more frequent among patients with concomitant AR, except in the >50 age class. In sum, patients' asthma appeared to be more severe when there was a concomitant diagnosis of AR [23].

The finding that AR is associated with an increased use of asthma-related medical services (this study, and the companion study with children) is consistent with evidence that treatment of AR is associated with reductions in asthma symptoms and medical service use. Several studies have shown that the pharmacological treatment of one of these conditions (asthma or AR) can alleviate the symptoms of the other [25]. Two retrospective cohort studies have provided observational evidence that pharmacological treatment of AR is associated with a significant reduction in the frequency of asthma-related emergency care [26, 27]. Further, experimental studies, however, will be required to verify that treatment directed at AR reduces asthma-related emergency care.

The longitudinal, observational design of this study and large sample size are strengths in determining the relationship between AR and medical resource use for asthma in general practice. The study has several limitations, however. A large sample size makes it possible to identify between-group differences that are statistically significant but not necessarily clinically meaningful. Nevertheless, we are confident that differences we found, related to the importance of AR as a comorbid condition with asthma, are clinically and economically meaningful (for instance, the effect of AR on the likelihood of asthma-related hospitalization exceeded the effect of increasing SABA prescriptions). ED visits are

infrequent and poorly recorded in the MediPlus[®] database and were pooled with hospitalizations, rather than being reported as a separate emergency care outcome. According to a 1997 survey, 43% of practices contributing to the MediPlus[®] database entered less than 50% of hospital discharge summaries. Hence, asthma-related hospitalizations might have been underreported. There is no indication, however, of a bias between the study groups in under-reporting of asthma-related hospitalizations.

Finally, the identification of AR was based on a recorded diagnosis or a prescription indicating AR, and this may have led to the prevalence being underestimated. Physician-diagnosed and -treated AR is likely to represent more severe disease, which is likely to be a marker for the poorer asthma outcomes noted. Further prospective studies on well-characterized cohorts would be needed to determine whether the tendency toward worse asthma outcomes applied also to milder and self-managed AR. The prescription drugs used to identify AR included systemic antihistamines and nasal corticosteroids. Systemic antihistamines might indicate conditions other than rhinitis but, in a sensitivity analysis, their exclusion from the list of drugs identifying AR had no substantive effect on the main study results: the prevalence of concomitant AR was reduced from 16.9% to 15.1%, while patients with concomitant AR still incurred significantly more asthma-related GP visits ($P < 0.0001$) and hospitalizations ($P = 0.012$) and higher drug costs ($P < 0.0001$). Prescriptions for nasal corticosteroids, however, might have indicated forms of rhinitis other than AR. It is likely that most rhinitis identified in this study was indeed allergic in origin, but this cannot be proven. Formal allergy testing is rarely done in the primary care setting in the United Kingdom and we have little specific information about the patients' atopic status.

Conclusions

In a cohort of 27 303 adults with asthma, patients with a recorded AR diagnosis and/or prescription generated significantly increased asthma-related medical resource use and drug costs. The co-existence of asthma and diagnosed or treated AR identifies a high-risk group of adult patients that should be targeted for care. A unified treatment strategy applied to patients with asthma and concomitant AR, as recommended in the ARIA guidelines, might reduce the costs of care for asthma.

Acknowledgements

Funding for this study was provided by Merck & Co. Inc. We thank Dr Alan Morrison for help in drafting this manuscript.

References

- 1 Global strategy for asthma management and prevention. Update from NHLB/WHO Workshop Report 1995. GINA. 2002. Revised 2002. NIH Publication No. 02-3659.
- 2 Prevalence of asthma treated in general practice. Factsheet 99/1. 1999. Lung & Asthma Information Agency.
- 3 Barnes PJ, Jonsson B, Klim JB. The costs of asthma. *Eur Respir J* 1996; 9:636–42.
- 4 Van Ganse E, Laforest L, Pietri G et al. Persistent asthma: disease control, resource utilisation and direct costs. *Eur Respir J* 2002; 20:260–7.
- 5 Kiivet RA, Kaur I, Lang A, Aaviksoo A, Nirk L. Costs of asthma treatment in Estonia. *Eur J Public Health* 2001; 11: 89–92.
- 6 Krahn MD, Berka C, Langlois P, Detsky AS. Direct and indirect costs of asthma in Canada, 1990. *Can Med Assoc J* 1996; 154:821–31.
- 7 Chew FT, Goh DY, Lee BW. The economic cost of asthma in Singapore. *Aust NZ J Med* 1999; 29:228–33.
- 8 Weiss KB, Sullivan SD, Lyttle CS. Trends in the cost of illness for asthma in the United States, 1985–1994. *J Allergy Clin Immunol* 2000; 106:493–9.
- 9 Stempel DA, Hedblom EC, Durcanin-Robbins JF, Sturm LL. Use of a pharmacy and medical claims database to document cost centers for 1993 annual asthma expenditures. *Arch Fam Med* 1996; 5:36–40.
- 10 Szucs TD, Anderhub H, Rutishauser M. The economic burden of asthma: direct and indirect costs in Switzerland. *Eur Respir J* 1999; 13:281–6.
- 11 Schwenkglenks M, Lowy A, Anderhub H, Szucs TD. Costs of asthma in a cohort of Swiss adults: associations with exacerbation status and severity. *Value Health* 2003; 6:75–83.
- 12 Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001; 108 (Suppl.):S147–334.
- 13 Malone DC, Lawson KA, Smith DH, Arrighi HM, Battista C. A cost of illness study of allergic rhinitis in the United States. *J Allergy Clin Immunol* 1997; 99 (Part 1):22–7.
- 14 Law AW, Reed SD, Sundry JS, Schulman KA. Direct costs of allergic rhinitis in the United States: estimates from the 1996 Medical Expenditure Panel Survey. *J Allergy Clin Immunol* 2003; 111:296–300.
- 15 Bousquet J, van Cauwenberge P, Khaltaev N and the Workshop Expert Panel. Allergic rhinitis and its impact on asthma. In collaboration with the World Health Organization. Executive summary of the workshop report, 7–10 December 1999, Geneva, Switzerland. *Allergy* 2000; 57:841–55.
- 16 Leynaert B, Neukirch F, Demoly P, Bousquet J. Epidemiologic evidence for asthma and rhinitis comorbidity. *J Allergy Clin Immunol* 2000; 106 (5 Suppl.):S201–5.
- 17 Bousquet J, Vignola AM, Demoly P. Links between rhinitis and asthma. *Allergy* 2003; 58:691–706.
- 18 Price DB, Ben-Joseph RH, Zhang Q. Changes in asthma drug therapy costs for patients receiving chronic montelukast therapy in the U.K. *Respir Med* 2001; 95:83–9.
- 19 Williams SG, Schmidt DK, Redd SC, Storms W. Key clinical activities for quality asthma care. Recommendations of the National Asthma Education and Prevention Program. *MMWR Recomm Rep* 2003; 52:1–8.
- 20 Desgagne A, Castilloux AM, Angers JF, LeLorier J. The use of the bootstrap statistical method for the pharmacoeconomic cost analysis of skewed data. *Pharmacoeconomics* 1998; 13: 487–97.
- 21 Thomas M, Zhang Q, Sazonov Kocevar V, Yin D, Price DB. Health care resource use by children with asthma and co-morbid allergic rhinitis in general practice in the United Kingdom. *Pediatrics* 2005; 115:129–34.
- 22 Yawn BP, Yunginger JW, Wollan PC, Reed CE, Silverstein MD, Harris AG. Allergic rhinitis in Rochester, Minnesota residents with asthma: frequency and impact on health care charges. *J Allergy Clin Immunol* 1999; 103 (Part 1):54–9.

- 23 Halpern MT, Schmier JK, Richner R, Guo C, Togias A. Allergic rhinitis: a potential cause of increased asthma medication use, costs, and morbidity. *J Asthma* 2004; 41:117–26.
- 24 Schramm B, Ehlken B, Smala A, Quednau K, Berger K, Nowak D. Cost of illness of atopic asthma and seasonal allergic rhinitis in Germany: 1-yr retrospective study. *Eur Respir J* 2003; 21:116–22.
- 25 Blaiss MS. Medical and economic dimensions linking allergic rhinitis and asthma. *Allergy Asthma Proc* 2002; 23:223–7.
- 26 Adams RJ, Fuhlbrigge AL, Finkelstein JA, Weiss ST. Intranasal steroids and the risk of emergency department visits for asthma. *J Allergy Clin Immunol* 2002; 109:636–42.
- 27 Crystal-Peters J, Neslusan C, Crown WH, Torres A. Treating allergic rhinitis in patients with comorbid asthma: the risk of asthma-related hospitalizations and emergency department visits. *J Allergy Clin Immunol* 2002; 109:57–62.